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COMMUNICATIONS

Aspirin-phenacetin interaction in the rat

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The absorptive and metabolic interactions of the analgesic mixture components phenacetin and caffeine and aspirin and caffeine in relation to their gross central nervous system (c.n.s.) effects have been examined by Collins et al (1977, 1979). Here, the drugs examined are aspirin and phenacetin.

Plasma concentrations of salicylate and/or phenacetin were determined after their administration to the female DA rat (180 ± 20 g) alone and in combination and c.n.s. effects were monitored by measuring locomotor activity. The apparatus and methodology used were as described by Collins et al (1977, 1979). The significance of differences between treatment means was assessed by Student's *t*-test.

Co-administration of phenacetin (50 mg kg^{-1}) and aspirin reduced the plasma salicylate concentrations attained (Table 1). This finding is in broad agreement with that of Coldwell et al (1974) which was attributed to a delay in absorption. There was also a progressive reduction in plasma phenacetin concentrations (Table 2) when increasing doses of aspirin were given together with a constant dose of phenacetin. Similar results were obtained by Thomas et al (1974) and were thought to be due to retention of phenacetin in the stomach.

Phenacetin (50 and 100 mg kg^{-1}) had no significant effect on locomotor activity (Table 3) which is in agreement with our previous finding (Collins et al 1977) that significant depression only occurred at a dose level of 200 mg kg^{-1}. Aspirin alone was also without consistent effect below 400 mg kg^{-1} when a pronounced and long-lasting stimulation was observed. This effect was not only enhanced but appeared with a lower dose of aspirin (200 mg kg^{-1}) when aspirin and phenacetin were given together. This finding is similar to but not so pronounced as that encountered with aspirin-caffeine mixtures (Collins et al 1979).

Locomotor activity has been found to involve central monoaminergic—especially dopaminergic—pathways (Svensson & Waldeck 1970). It was suggested (Collins et al 1979) that aspirin-induced hyperactivity might be due to effects exerted on these mechanisms either directly (Paalzow 1973) and/or indirectly via prostaglandin synthetase inhibition (Laborit et al 1975). It was also suggested that in the presence of a phosphodiesterase inhibitor, such as caffeine, salicylate effects on catecholamine utilization might be augmented as was shown experimentally.

Table 1. Mean plasma concentrations of salicylate ± s.e. attained after oral administration of aspirin and phenacetin to the female DA rat (n = no. of rats).

Drug & dose (mg kg^{-1})	Mean plasma concn (mg $litre^{-1}$) ± s.e. 0·5h	1h	2h	4h	6h	8h
Aspirin (100) n = 10	235·1 ± 12·6	250·5 ± 11·0	181·5 ± 16·3	180·3 ± 11·7	152·5 ± 12·6	131·8 ± 11·6
Aspirin (100) + phenacetin (50) n = 5	226·5 ± 12·7	242·7 ± 24·2	127·1* ± 8·9	176·5 ± 12·8	128·1 ± 16·6	171·6 ± 19·6
Aspirin (200) n = 5	342·5 ± 13·6	308·2 ± 15·5	326·7 ± 16·0	290·2 ± 4·9	317·6 ± 13·4	268·6 ± 14·8
Aspirin (200) + phenacetin (50) n = 5	254·6** ± 18·5	274·5 ± 5·3	271·9 ± 19·9	253·5 ± 12·8	268·7* ± 11·5	266·2 ± 9·0
Aspirin (400) n = 5	525·3 ± 20·2	556·1 ± 10·1	427·5 ± 23·9	389·2 ± 9·9	311·8 ± 12·4	359·2 ± 18·2
Aspirin (400) + phenacetin (50) n = 5	419·2* ± 25·0	387·5* ± 50·7	361·7 ± 21·0	373·3 ± 5·8	397·2** ± 11·9	357·4 ± 27·4

*$P < 0.05$, **$P < 0.01$ (differences from aspirin alone)

Table 2. Mean plasma phenacetin concentrations ± s.e. attained after oral administration of phenacetin and aspirin to the female DA rat. Each result is the mean from 5 animals.

Drug & dose (mg kg^{-1})	0·5h	1h	2h
Phenacetin (50)	12·48 ± 1·02	5·04 ± 0·45	1·11 ± 0·02
Phenacetin (50) + aspirin (100)	6·85 ± 1·05**	3·89 ± 0·43	1·05 ± 0·01
Phenacetin (50) + aspirin (200)	4·15 ± 0·44***	3·58 ± 0·44*	1·06 ± 0·02
Phenacetin (50) + aspirin (400)	4·74 ± 0·69***	3·54 ± 0·44*	1·08 ± 0·02

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ (differences from phenacetin data.

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Table 3. Mean locomotor activity (± s.e.) of female DA rats during the first 8-hourly intervals after drug administration.

Drug dose (mg kg^{-1})	No. of experiments	Square root transformation (Steel & Torrie 1960) of the mean activity count (± s.e.) Time after drug administration (h) 0–1	1–2	2–3	3–4	4–5	5–6	6–7	7–8
Suspending agent	22	36·86 ± 1·33	22·34 ± 0·90	19·48 ± 1·17	15·89 ± 1·02	14·96 ± 0·92	13·50 ± 0·91	14·18 ± 1·21	15·59 ± 1·02
Aspirin 50	15	39·64 ± 1·25	21·57 ± 1·20	20·88 ± 1·29	17·43 ± 1·37	14·96 ± 1·06	13·38 ± 1·21	14·39 ± 1·51	15·20 ± 0·99
Aspirin 100	17	39·32 ± 1·24	22·70 ± 1·10	20·35 ± 1·15	19·81* ± 1·21	14·63 ± 1·25	18·00* ± 1·13	12·70 ± 1·00	14·89 ± 1·55
Aspirin 200	15	39·73 ± 1·62	23·64 ± 1·36	19·24 ± 1·33	18·49 ± 1·42	15·43 ± 1·63	14·07 ± 1·56	16·38 ± 1·20	12·74* ± 0·88
Aspirin 400	19	41·21 ± 1·73	28·14* ± 1·96	24·99** ± 1·35	21·68** ± 1·42	18·28 ± 1·43	18·19* ± 1·67	15·03 ± 1·18	16·68 ± 1·40
Phenacetin 50	8	35·35 ± 4·32	19·04 ± 2·73	18·65 ± 1·60	15·24 ± 2·03	16·07 ± 1·80	13·92 ± 1·45	13·73 ± 1·26	17·32 ± 2·61
Phenacetin 100	8	38·19 ± 1·40	20·68 ± 1·67	20·76 ± 1·61	16·21 ± 2·29	16·33 ± 2·24	13·59 ± 1·57	13·95 ± 1·32	16·84 ± 1·74
		Time after drug administration (h) 0–1	1–2	2–3	3–4	4–5	5–6	6–7	7–8
Aspirin 50 + Phenacetin 50	10	38·12 ± 2·11	22·05 ± 1·03	16·36 ± 1·26	16·59 ± 0·97	13·23 ± 1·02	11·05* ± 0·52	12·76 ± 2·02	13·31 ± 1·08
Aspirin 100 + Phenacetin 50	17	38·18 ± 1·19	23·11 ± 1·31	20·03 ± 1·02	17·85 ± 1·66	14·41 ± 1·37	13·98 ± 1·03	16·15 ± 1·25	14·60 ± 1·39
Aspirin 200 + Phenacetin 50	17	38·72 ± 2·48	29·37** ± 2·06	28·64*** ± 1·66	23·71*** ± 1·56	22·39*** ± 1·10	18·08** ± 1·38	18·58** ± 1·02	16·82 ± 1·35
Aspirin 400 + Phenacetin 50	14	43·34** ± 1·25	31·09*** ± 1·68	26·32** ± 1·73	24·68** ± 20·49	20·93** ± 1·96	18·19* ± 1·54	17·61 ± 1·81	16·95 ± 1·24
Aspirin 100 + Phenacetin 100	6	40·35 ± 1·53	22·72 ± 1·94	18·41 ± 2·55	17·67 ± 2·18	19·73* ± 1·92	13·82 ± 2·73	14·86 ± 1·80	14·45 ± 1·60
Aspirin 400 + Phenacetin 100	11	44·02** ± 1·95	33·48*** ± 1·72	31·94*** ± 2·70	21·89* ± 2·31	20·43** ± 1·72	21·73*** ± 1·78	16·60 ± 2·18	15·01 ± 1·53

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.01$ (difference from control values).

Phenacetin has also been shown (Lozada et al 1972) to possess phosphodiesterase inhibitor activity and it is conceivable that a similar mechanism whereby hyperactivity appeared with lower doses of aspirin than were effective when given alone might be operative. Moreover, paracetamol, which is the major metabolite of phenacetin (Dubach & Raaflaub 1969), has been shown to be a selective inhibitor of prostaglandin synthetase in the c.n.s. and thus might also be capable of augmenting the effects of aspirin on locomotor activity.

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